against cancer. But that conclusion is far from certain, says Prives.

One problem is that no one knows what 53PB2 might do in the cell. What's more, work by pediatric oncologist Louie Naumovski at Stanford Medical School shows that the protein is not located in the nucleus, which would imply that it does not influence p53 binding to the DNA but may help bring p53 to the nucleus or fold correctly.

No matter what 53BP2 does relative to p53, Pavletich suggests that the binding is worth studying for its molecular details. The protein uses two motifs to link up with p53: a series of ankyrin repeats—four copies of a set of 30-some amino acids—and another loop called an SH3 domain. A multitude of other proteins use ankyrin motifs for binding, but they've never before been seen in action. Pavletich's colleagues agree that these details would be worth pursuing even if p53 didn't have such a key role in cancer. Says structural biologist Iris Mastrangelo at Brookhaven National Laboratory in New York, "p53 has exquisite molecular mechanisms that [allow] these specialized parts of the protein to target quite different molecules." Indeed, the new results may only feed researchers' p53 obsession.

–Elizabeth Pennisi

PHYSIOLOGY RESEARCH

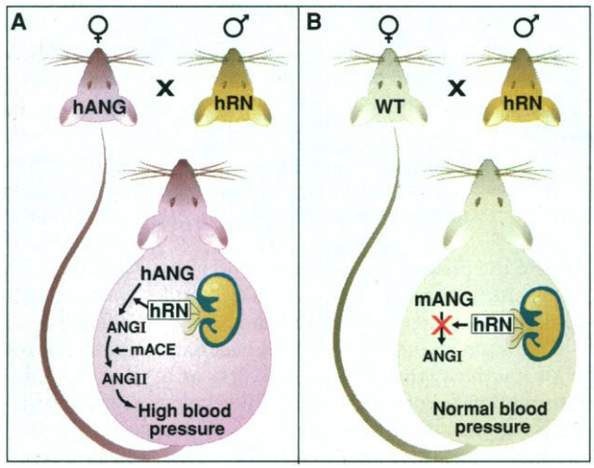
Mouse Model for Pregnancy Problem?

For women and physicians alike, one of the most vexing problems of pregnancy is a condition known as pregnancy-induced hypertension (PIH). Developing in the last trimester, PIH can send the expectant mother's blood pressure rocketing, damaging her kidney, liver, and heart, and putting both her life and that of the child she is carrying at risk. No one knows what causes PIH, which affects up to 10% of human pregnancies and causes the majority of pregnancy-related complications. And efforts to study the condition, as well as to develop therapies for it, have been handicapped by lack of an animal model that reproduces the pathological features of PIH. New work by Akiyoshi Fukamizu and his colleagues at the University of Tsukuba, Japan, may change that.

On page 995, the investigators report that they may have stumbled onto a new strategy for simulating PIH in mice. They did this by mating mice, each of which had been genetically altered to carry one of two genes that encode proteins involved in blood pressure control. One makes angiotensinogen, the precursor of the potent blood pressure–raiser angiotensin II, and the other makes renin, the enzyme that releases angiotensin II from the precursor. When the right mating combination brought these two proteins together in pregnant females, they developed high blood pressure and other changes reminiscent of PIH.

While those who study PIH say that the disease might not be caused the same way in humans, they nevertheless think the model may shed light on the mechanisms by which high blood pressure wreaks havoc on both mother and fetus. Ultimately, such an understanding might lead to better therapies for PIH, which currently can only be cured by premature delivery. In addition, the same strategy might also be used to study other pregnancy-related conditions brought on by a combination of maternal and fetal factors. Indeed, says Charles Rosenfeld, a neonatologist and PIH researcher at the University of Texas Southwestern Medical School in Dallas, "It's probably some of the most innovative work I have seen in a long time in this field."

Fukamizu did not set out to develop a mouse model of PIH. When he began the experiments 7 years ago, he recalls, his goal was to develop mice that could be used to study how renin and angiotensinogen might lead to high blood pressure. To do that, he and his colleagues genetically engineered one mouse strain with the human gene for angiotensinogen and another with the human renin gene. The idea was that when mice with the renin gene were mated with animals with the human angiotensinogen gene, overexpression of the two genes in the progeny would cause high blood pressure.



PIH in mice? Human renin (hRN) from the placenta raises the blood pressure of mice making human angiotensinogen (hANG), but not of those making the mouse protein (mANG).

When his group paired female renin transgenics with male angiotensinogen transgenics, the resulting pups were in fact born hypertensive. But when Fukamizu tried the reverse combination—females with the human angiotensinogen gene and males with the renin gene—he noticed a surprising result: The mothers died late in gestation. "I noticed that there was something there," says Fukamizu. When they studied more of the same kinds of matings, Fukamizu's group found that the pregnant mice displayed such PIH symptoms as placental and heart problems, as well as high urine protein levels, an indicator of damaged kidneys.

These observations suggested that human renin, produced by the paternal gene in the placenta, which is derived from fetal tissue, was making its way into the mother mouse's circulatory system. There it could act on the human angiotensinogen, leading to progressively increasing hypertension. Fukamizu checked that idea by mating male human renin–producers with normal females and looking for renin in females' bloodstream. He found it, which "shows you that the placenta, at least in this model, plays a very prominent role in the development of maternal hypertension," Rosenfeld says.

The big question now is whether the mouse model does, in fact, reflect what's happening in human PIH. One thing giving pause to other researchers are some puzzling features of the model, including the fact that PIH does not develop if females overexpressing human renin are mated with males that overproduce human angiotensinogen. What's more, they note that human placentas may not have the ability to transmit renin into the maternal circulation as mouse placentas do. PIH experts also note that while the increased blood pressure in the mice is presumably due to their increased production of human angiotensin II, the protein's levels are not always high in humans who have either PIH or preeclampsia, an almost identical hypertensive condition of pregnancy. All in all, says PIH researcher Phyllis August at Cornell University Medical Center in New York, "I don't know what this [model] tells you about preeclampsia."

Despite these questions, researchers say the Fukamizu team's model can still be used to study the biochemistry of the disorder in further detail and, quite possibly, to examine the effects of blood pressure drugs and other therapies. "This is not the perfect model, but it can give us some insights," Rosenfeld concludes.

–Trisha Gura

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